UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,233	01/13/2004	Poul Egon Bertelsen	55682CON(71432)	5334

21874 7590 07/13/2011

EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
SASAN, ARADHANA	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
07/13/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/758,233	BERTELSEN ET AL.
	Examiner	Art Unit
	ARADHANA SASAN	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68,71,72,75-80,82,83,88-96,108,109,111,115,116,119,121,123 and 125* is/are rejected.

7)☒ Claim(s) *82* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 68,71,72,75-80,82,83,88-96,108,109,111,115,116,119,121,123 and 125.

DETAILED ACTION

Status of Application

1. The remarks, amendments, and Request for Continued Examination filed on 06/16/11 are acknowledged.

2. Claims 1-67, 69, 70, 73, 74, 81, 84-87, 97-107, 110, 112-114, 117-118, 120, 122, 124, and 126 are cancelled.

3. Claims 68, 71, 72, 75, 88-89, 91-96, 109, and 11 were amended.

4. Claims 68, 71-72, 75-80, 82-83, 88-96, 108-109, 111, 115-116, 119, 121, 123, and 125 are included in the prosecution.

Continued Examination under 37 CFR 1.114

5. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/16/11 has been entered.

Response to Arguments and Declaration

Rejection of claims under 35 USC § 103(a)

6. Applicant's arguments, see Page 7, filed 06/16/11, with respect to the rejection of claims 68, 70-72, 75-80, 82, 83, 85-86, 91-92, 95-96, 108, 109, 111 and 119-126 under 35 U.S.C. 103(a) as being unpatentable over Nemoto et al. (JP 03-240729) in view of

Klioze et al. (US 2,887,439) have been fully considered and are persuasive in light of the amendment of claim 68 to incorporate the limitation of “lornoxicam or a pharmaceutically acceptable salt, complex or prodrug thereof" from claim 87.

Therefore the rejection withdrawn. However, upon further consideration, a new ground(s) of rejection is made over Nemoto et al. (JP 03-240729) in view of Klioze et al. (US 2,887,439) and Penkler et al. (US 5,854,226).

7. Applicant’s arguments with respect to the rejection of claims 87-90, 93-94 and 115-118 under 35 U.S.C. 103(a) as being unpatentable over Nemoto et al. (JP 03-240729) in view of Klioze et al. (US 2,887,439) and Penkler et al. (US 5,854,226) have been fully considered.

In light of the cancellation of claim 87, the rejection with respect to this claim is rendered moot.

In light of the amendment of claim 68 to incorporate the limitation of “lornoxicam or a pharmaceutically acceptable salt, complex or prodrug thereof" from claim 87, Applicant’s arguments (as they apply to amended claim 68) are not found persuasive.

Applicant argues that Nemoto provides compositions comprising chlortenoxicam with solubility test results and does not provide compositions comprising lornoxicam or a pharmaceutically acceptable salt, complex or prodrug thereof. Applicant refers to the Declaration filed by one of the inventors Poul Bertelsen in which the dissolution of a composition, comprising lornoxicam and prepared according to the teachings of Nemoto, was tested using the method required in the claims of the instant invention, the results are provided in Appendix A of the Declaration. “After 1 hour, the composition,

prepared according to the teachings of Nemoto and comprising a 1:5 ratio of lornoxicam to antacid, was found to release only 37.8% in 0.07N HCl. Therefore, the amount released after 20 minutes must have been less than 50% as required by the instant claims. As the composition comprising lornoxicam and prepared according to Nemoto does not meet the dissolution requirement of the claim, Nemoto cannot render the instant claim obvious."

Applicant argues that the methods described by Nemoto (i.e., conventional granulation) cannot produce compositions comprising lornoxicam which would achieve the dissolution requirements of the claimed invention.

This is not persuasive because Nemoto is not relied upon for teaching lornoxicam. Nemoto is relied upon for teaching an oral granule preparation containing an antacid and an oxicam drug. The deficiency in Nemoto regarding the specific oxicam drug, lornoxicam, is cured by Penkler. The deficiency in Nemoto regarding the mean particle size of at the most 250 micrometers of the granules is cured by Klioze. The three references are properly combined because one of ordinary skill in the art would find it obvious to substitute lornoxicam for the oxicams used by Nemoto with a reasonable expectation of success and because Klioze teaches that granules ranging from about 20 to 100 mesh (or 149 µm to 840 µm) are most advantageous in preparing palatable, rapidly disintegrable tablets comprising compressed granules.

Therefore, the rejection over Nemoto, Klioze and Penkler is applied towards the amended claims.

Claim Objections

8. Claim 82 is objected to under 37 CFR 1.75(c) as being in improper form because it is dependent on claim 108, which is not a preceding claim. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 68, 71-72, 75-80, 82-83, 88-96, 108-109, 111, 115-116, 119, 121, 123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nemoto et al.

(JP 03-240729) in view of Klioze et al. (US 2,887,439) and Penkler et al. (US 5,854,226).

The claimed invention is a quick release pharmaceutical composition for oral administration lornoxicam or a pharmaceutically acceptable salt, complex or prodrug thereof, the composition being in the form of a particulate composition or being based on a particulate composition, wherein either the particles of the particulate composition used in the manufacture of the composition have a mean particle size of the most 250 micrometers, or at least 50% w/w of the particles of the particulate composition used in the manufacture of the composition pass through a 180 micrometer sieve; wherein the quick release pharmaceutical composition contains the active substance in contact with an alkaline substance; and the composition, when tested in accordance with the dissolution method I defined herein employing 0.07N hydrochloric acid as dissolution medium, releases at least 50% w/w of the active substance within the first 20 minutes of the test.

Nemoto teaches “an oral solid preparation containing one or more types of antacids that accelerates the absorption of oxicam antiinflammatory drugs” (Page 1, claim 1). Sodium hydrogen carbonate is disclosed as the antacid (Page 1, claim 3). The antacid “accelerates the absorption of oxicam antiinflammatory drugs” (Page 2). Granules of the antacid and oxicam antiinflammatory drug are disclosed (Page 3). The granules are formed in a mixture of alcohol and purified water (Page 4). Capsules and tablets are manufactured by adding a lubricant to the granules (Page 4). The solubility

of the prepared tablets in artificial gastric juice was greater than 50% within 20 minutes of the test (Page 9, Table 3). The granules were graded to 20 mesh (Page 5).

Nemoto does not expressly teach a mean particle size of at the most 250 micrometers of the granules.

Klioze teaches a tablet that may be swallowed whole, chewed, dissolved in the mouth, or dissolved or suspended in liquids (Col. 2, lines 6-12). This rapidly disintegrating tablet comprises a plurality of compressed granules containing sweetening agents and perhaps a filler (Col. 2, lines 13-20). The granules used in the tablets are screened "to insure that they are of an optimum size for the formation of tablets. It has been found that granules ranging from about 20 to 100 mesh (U.S. Sieve Series) are most advantageous in preparing the tablets of this invention" (Col. 2, lines 41-46). 20 mesh corresponds to 0.84mm or 840μm and 100 mesh corresponds to 0.149mm or 149μm (see Page 1544 of Remington's 16th Edition 1980, as provided by Applicant on 09/15/08). Therefore, Klioze teaches the formation of rapidly disintegrating tablets comprising granules that are between 149μm and 840μm, thereby rendering the instant claims with the limitation of the mean particle size of the particles of the particulate composition at the most 250μm obvious to one of ordinary skill in the art.

Nemoto and Klioze do not expressly teach lornoxicam as the active substance.

Penkler teaches a pharmaceutical composition for oral administration comprising an inclusion complex of a non-steroidal anti-inflammatory drug, including lornoxicam (Col. 5, lines 66-67), an alkaline earth metal bicarbonate, and further active ingredients (Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an oral granule preparation containing an antacid and an oxicam drug, as suggested by Nemoto, reduce the granule size to a range between 149μm and 840μm, as taught by Klioze, use lornoxicam as the drug along with an alkaline earth metal bicarbonate, as suggested by Penkler, and produce the instant invention.

One of ordinary skill in the art would do this because the use of lornoxicam in a pharmaceutical composition with an alkaline earth metal bicarbonate is known, as evidenced by Nemoto and Penkler. One with ordinary skill in the art would find it obvious to substitute lornoxicam for the oxicams used by Nemoto during the process of routine experimentation with a reasonable expectation of success in producing a functional pharmaceutical composition comprising lornoxicam and an alkaline earth metal bicarbonate. Moreover, Klioze teaches that granules ranging from about 20 to 100 mesh (or 149μm to 840μm) are most advantageous in preparing palatable, rapidly disintegrable tablets comprising compressed granules (as taught by Klioze). One of ordinary skill in the art would have a reasonable expectation of success in producing functional rapidly disintegrable tablets with granule size between 149μm to 840μm.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 68, the limitation of lornoxicam would have been obvious over the oxicams taught by Nemoto (Page 1, claim 1) and the lornoxicam taught by Penkler (Col. 5, lines 66-67). The limitation of the active substance in contact with the alkaline substance and the limitation of a particulate composition would have been obvious over the granules of antacid and oxicam disclosed by Nemoto (Page 3). The limitation of the dissolution method employing 0.07N HCl acid as dissolution medium would have been obvious over the artificial gastric juice (with an acidic pH) taught by Nemoto (Page 9, Table 3). The limitation of the mean particle size of at the most 250 micrometers would have been obvious over the granules of antacid and oxicam disclosed by Nemoto (Page 3) in view of the final particle size of granules between 149μm and 840μm as taught by Klioze (Col. 2, lines 41-46).

Regarding instant claim 71, the limitation of at least 55% w/w release would have been obvious over the solubility of preparations 3-9 as disclosed by Nemoto (Page 9, Table 3).

Regarding instant claim 72, the solubility of the active substance would have been obvious over the oxicam actives taught by Nemoto (Page 1, claim 1) and the lornoxicam taught by Penkler (Col. 5, lines 66-67).

Regarding instant claims 75-79, the limitation of an excipient would have been obvious over the calcium hydrogen phosphate taught by Nemoto (Page 6, Embodiment 9).

Regarding instant claim 80, the limitation of the particle size of the filler would have been obvious over the calcium hydrogen phosphate taught by Nemoto (Page 6,

Embodiment 9). One with ordinary skill in the art would modify the particle size of the filler during the process of routine optimization and the recited particle size (140 μm) would have been an obvious variant unless there is evidence of criticality or unexpected results.

Regarding instant claims 82-83, 95-96 and 108, the antacid would have been obvious over the sodium hydrogen carbonate and calcium hydrogen phosphate disclosed by Nemoto (Page 1, claim 3). The limitation of the mean particle size of the antacid-like substance would have been obvious because one with ordinary skill in the art would vary the particle size of the antacid during the process of routine experimentation depending on the desired attributes of the composition and over the final particle size of granules between 149μm and 840μm as taught by Klioze (Col. 2, lines 41-46). The recited particle size (at the most 297 μm) would have been an obvious variant unless there is evidence of criticality or unexpected results.

Regarding instant claims 88-90, the further active drug substance would have been obvious over the further active drug substance, including paracetamol as taught by Penkler (Col. 8, lines 9-12).

Regarding instant claims 91-92, the dosage of the active substance would have been obvious over the 2mg of chlortenoxicam and tenoxicam disclosed by Nemoto (Page 5, Table 1).

Regarding instant claim 93, the dosage of the active substance would have been obvious over the unit compositions of lornoxicam (4mg) taught by Penkler (Figure 2).

One with ordinary skill in the art would vary the dosage of the active ingredient, lornoxicam, in order to optimize the release/dissolution profile, and stability.

Regarding instant claim 94, the water content limitation would have been obvious over the drying step (after the addition of water and mixing steps) as taught by Penkler (Col. 4, line 9). A person skilled in the art would reduce the water content of the composition in order to improve shelf life and minimize interactions and leaching, therefore, the water content limitation would have been an obvious variant found during routine optimization.

Regarding instant claim 109, the dissolution test would have would have been obvious over the artificial gastric juice (with an acidic pH) taught by Nemoto (Page 9, Table 3). A person skilled in the art would have found it obvious to test the dissolution/release of the active at various pH levels (especially acidic pH levels which are present in gastric conditions) during the process of routine optimization to ensure the release of the active ingredient.

Regarding instant claim 111, the coated tablet would have been obvious over the coating of tablets taught by Nemoto (Page 4, 2nd full paragraph).

Regarding new claims 115-116, the limitation of lornoxicam would have been obvious over the lornoxicam taught by Penkler (Col. 5, lines 66-67). The limitation of sodium hydrogen carbonate would have been obvious over the sodium hydrogen carbonate disclosed by Nemoto (Page 1, claim 3). The limitation of microcrystalline cellulose would have been obvious over the microcrystalline cellulose disclosed by

Nemoto (Page 5, Table 1). The limitation of calcium hydrogen phosphate anhydrous would have been obvious over the calcium hydrogen phosphate disclosed by Nemoto (Page 1, claim 3). The limitations of L-HPC and hydroxy propyl cellulose would have been obvious over the low substituted hydroxypropyl cellulose and the hydroxypropyl cellulose disclosed by Nemoto (Page 5, Table 1). The limitations of water and ethanol would have been obvious over the mixture of alcohol and purified water disclosed by Nemoto (Page 4, lines 5-6). The limitation of calcium stearate would have been obvious over the calcium stearate disclosed by Nemoto (Page 4, line 12).

Regarding claim 119, the limitation of the composition having mechanical strength to enable the composition to be coated using traditional coating equipment would have been obvious over the coating of tablets taught by Nemoto (Page 4, 2nd full paragraph).

Regarding claim 121, the limitation of the composition further comprising a filler having binding properties would have been obvious over the calcium hydrogen phosphate disclosed by Nemoto (Page 1, claim 3). The crushing strength limitation is a functional limitation which is rendered obvious by the tablet comprising granules as taught by Nemoto in view of the granules taught by Klioze. One of ordinary skill in the art would find it obvious to determine the crushing strength of the tablets during the process of routine experimentation and the recited crushing strength of at least about 50N would have been an obvious variant unless there is evidence of criticality or unexpected results.

Regarding instant claim 123, the limitation of the composition that passes through a 180 micrometer sieve would have been obvious over the granules that are between 149μm and 840μm, as taught by Klioze (Col. 2, lines 41-46).

Regarding instant claim 125, the limitations of the granulate would have been obvious over the granules of the antacid and oxicam antiinflammatory drug taught by Nemoto (Page 3).

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached at 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615